Original Article

Language and Cognition in Childhood Acute Lymphocytic Leukemia (ALL): Understanding Chemotherapy-Related Neurocognitive Changes

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ABSTRACT

Purpose: This study aimed to determine whether chemotherapy affects cognitive and verbal abilities in children with acute lymphocytic leukemia (ALL). Given that chemotherapy can have neurotoxic consequences, especially on the developing brain, this study sought to evaluate any effects on language ability, memory, attention, and general cognitive function in young ALL survivors.

Method: From 2021 to 2024, 45 children aged 5-6 diagnosed with childhood acute lymphocytic leukemia (ALL) were recruited from the phoniatrics clinic, Center of Medical Excellence, at the National Research Center (NRC) in Cairo, Egypt. All children's cognitive and language skills were assessed using the REAL Scale and IQ before starting chemotherapy and then again four months after chemotherapy.

Result: This study's results demonstrate how chemotherapy affects children with ALL regarding their cognitive and linguistic abilities. Some children showed deterioration in verbal fluency, executive function, and language processing. The results showed a strong positive correlation between the change in Total RLS, ELS, and TLS and the change in Full-Scale IQ.

Conclusion: This study shows that pediatric leukemia chemotherapy can significantly affect a child's cognitive and linguistic development. Some children may notice a decline in executive functions, word retrieval, and fluency. These findings demonstrate the need for targeted cognitive-linguistic rehabilitation programs to support language development in cancer survivors. Future studies should continue to investigate efficient intervention techniques to lessen the neurocognitive effects of chemotherapy and improve the lives of children who have survived leukemia.

Key Words: Chemotherapy, cognitive, leukemia, speech and language.

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INTRODUCTION

About 30% of pediatric cancers globally are leukemias, making it the most prevalent childhood malignancy[1]. Chemotherapy-induced cognitive impairment (CICI), sometimes known as "chemobrain," is a term used to describe the long-term neurocognitive problems that may result from these therapies, even though advances in chemotherapy have significantly increased survival rates[2]. Little is known regarding chemotherapy's precise effects on language processing and communication abilities in children receiving leukemia treatment, even though most of the work has been on memory, attention, and executive function deficiencies[3].

The functional integrity of neuronal networks in the hippocampus, temporal lobes, and prefrontal cortex is essential for language and cognition, which have complex connections[4]. Chemotherapy drugs, including methotrexate and cytarabine, have been linked to neurotoxicity, white matter damage, and decreased neurogenesis in children with leukemia, all of which may impair cognitive-linguistic ability[5]. According to longitudinal research, children undergoing chemotherapy may show delayed language acquisition, decreased verbal fluency, and impaired discourse structure[6,7]. These findings imply that chemotherapy impairs the brain's capacity to process and generate language effectively.

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Chemotherapy also impairs executive control, working memory, and processing speed, which can tangentially lead to language issues. Syntactic processing, verbal understanding, and spontaneous speech production are all necessary for these cognitive functions. Furthermore, research suggests that younger kids, whose brains are still growing, can be particularly vulnerable to the neurocognitive effects of chemotherapy, which could lead to long-term issues with communication and academics[8].

The effects of chemotherapy on language processing and cognitive function are not limited to immediate concerns; they often persist long after the conclusion of treatment. Individuals who have survived childhood leukemia may encounter challenges in complex verbal tasks, particularly those that necessitate advanced executive functions, including thought organization, multitasking, and the generation of suitable responses. The chemotherapy effect impacts verbal and social communication, academic outcomes,s, and mental health, and some children require ongoing therapy support[9,10]. These challenges emphasize the importance of individualized educational programs that tackle the needs of children with ALL.

The possibility of neuroplasticity in kids getting treatment is a positive way for them to get better, even though chemotherapy can cause problems. Cognitive retraining programs early may help with some of the mental difficulties of chemotherapy. These treatments help with functional adaptation and neural repair, letting kids regain skills they've lost or develop ways to compensate for their cognitive problems[11,12]. As more study is done, these results will be used in clinical settings to improve the long-term outcomes for young people who have survived leukemia, especially when it comes to mental and language recovery.

This study intends to investigate the connection between chemotherapy, language processing, and cognitive function in children with leukemia in light of these worries. In particular, we look into the effects of four months of chemotherapy on juvenile patients' language and general cognitive skills. To assist the cognitive-linguistic development of pediatric leukemia survivors, early intervention measures and customized rehabilitation programs must take into account these neurocognitive abnormalities.

SUBJECTS AND METHODS

Forty-five children aged 5-6 diagnosed with childhood acute lymphocytic leukemia (ALL) were referred by their oncologist to the phoniatrics clinic, Center of Medical Excellence, at the National Research Center (NRC), Cairo, Egypt, from 2021 to 2024. All children's cognitive and language skills were assessed using the REAL Scale and IQ before starting chemotherapy and then repeated four months after chemotherapy.

The REAL Scale[13] is a comprehensive tool for evaluating Arabic language skills. It consists of a battery of tests assessing receptive and expressive language skills in Arabic-speaking children aged five to 12 years and 11 months. The Scale was administered in a single session lasting approximately 90 minutes. Some children required a 10-minute break during the assessment, while others did not. The REAL Scale is a validated Arabic test, with correlation studies conducted between the tested parameters and the participants' ages to establish its construct validity. Receptive tasks and expressive tasks were also correlated to demonstrate convergent validity.

Additionally, receptive subtests were highly correlated with expressive ones, to some extent, when they were used to measure the language skills of a typically developing child. Cronbach's alpha of the REAL scale subsets ranged from 0.673 to 0.901. The test-retest stability coefficient ranges from 0.775 to 0.975 for the different subsets. A percentile rank of 70 or more indicates satisfactory Arabic language development.

The Stanford-Binet Intelligence Scales (SB-5), Fifth Edition[14], was used to ensure that all the children had an average IQ and to correlate any improvement after therapy with IQ subtests. The SB-5 measures the intellectual and cognitive ability of examinees aged 2-85 years and older. In addition to a full-scale score, it covers five factors of mental ability: fluid reasoning, quantitative reasoning, visual-spatial reasoning, working memory, and knowledge.

RESULTS

(Table 1) shows the Receptive Language Score (RLS) before and after treatment, indicating that RLS, Total RLS, and Percentile Rank RLS decreased significantly after treatment. (Table 2) shows the Expressive Language Score (ELS) before and after treatment, also indicating that ELS, Total ELS, and Percentile Rank ELS decreased significantly after treatment. In (Table 3), Total Language Score (TLS) before and after treatment showed that TLS, Total TLS, and Percentile Rank TLS decreased significantly after treatment. (Table 4) shows the full IQ scale, and all subscales decreased significantly after treatment.

(Table 5) shows a strong positive correlation exists between the change in Total RLS, ELS, and TLS and the change in Full-Scale IQ. (Table 6) shows that the REAL Scale change and IQ did not correlate with age or sex.

(Figure 1) Shows changes in Language scores after Chemotherapy, and (Figure 2) shows IQ scale change after chemotherapy.

Table 1: RLS before and after treatment showed three variables decreased significantly after treatment:

	Paired Differences				
	Mean	95% Confidence Interval of the Difference		*T*	*p-value*
		Lower	Upper		
RLS Before – nRLS After	2.44	.14	4.75	2.139	.038
Total RLS Before – nTotal RLS After	1.98	.11	3.84	2.135	.038
Percentile Rank RLS Before –nPercentile Rank RLS After	2.44	.14	4.75	2.141	.038

Table 2: ELS before and after treatment shows three variables decreased significantly after treatment:

	Paired Differences				
	Mean	95% Confidence Interval of the Difference		*t*	*p-value*
		Lower	Upper		
ELS Before – ELS After	4.84	.69	9.00	2.348	.023
Total ELS Before – Total ELS After	1.96	.26	3.65	2.326	.025
Percentile Rank ELS Before – Percentile Rank ELS After	4.67	.95	8.38	2.533	.015

Table 3: TLS before and after treatment, showed three variables decreased significantly after treatment:

	Paired Differences				
	Mean	95% Confidence Interval of the Difference		*T*	*p-value*
		Lower	Upper		
TLS Before – TLS After	6.58	.85	12.31	2.315	.025
Total TLS Before –	1.96	.26	3.65	2.324	.025
Percentile Rank TLS Before – Percentile Rank TLS After	4.00	.65	7.35	2.404	.020

Table 4: The full- IQ scale and all subscales decreased significantly after treatment:

	Paired Differences				
		95% Confidence Interval of the Difference		*t*	*p-value*
	Mean	Lower	Upper		
Full-Scale IQ Before – Full-Scale IQ After	3.4	.3	6.4	2.246	.030
Nonverbal IQ Before – Nonverbal IQ After	3.2	.2	6.2	2.157	.037
Verbal IQ Before – Verbal IQ After	3.4	.4	6.5	2.275	.028
Fluid reasoning Before – Fluid reasoning After	2.2	.0	4.3	2.048	.047
Knowledge Before – Knowledge After	4.4	.3	8.6	2.175	.035
Quantitative Reasoning Before – Quantitative Reasoning After	3.9	.5	7.3	2.319	.025
Visual-Spatial Reasoning Before – Visual-Spatial Reasoning After	1.4	.0	2.8	2.083	.043
Working Memory Before – Working Memory After	3.6	.4	6.7	2.275	.028

Table 5: A strong positive correlation exists between the change in Total RLS, ELS, and TLS and the change in Full-Scale IQ:

		Change IQ Full	
		r	*P*
Spearman's rho	Change RLS	.921	.000
	Change ELS	.919	.000
	Change TLS	.918	.000

Table 6: The REAL Scale change and IQ did not correlate with age or sex:

		Age	
		r	*P*
Spearman's rho	Change or Total RLS	-.063	.683
	Change of Total ELS	-.243	.107
	Change of Total TLS	-.241	.110
	Change of IQ Full scale	-.181	.234

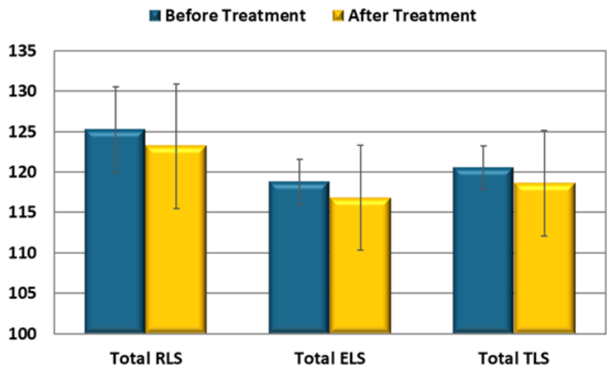

Fig. 1: Showing changes in Language scores after Chemotherapy

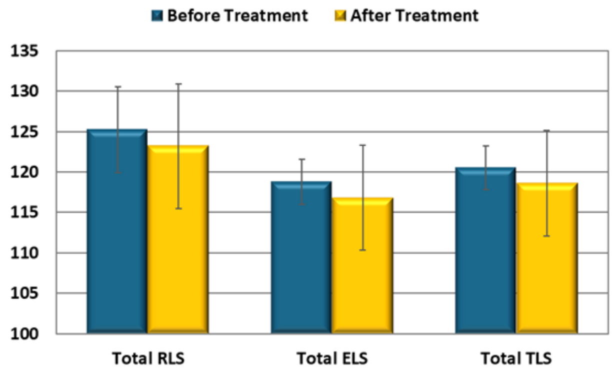

Fig. 2: Showing IQ scale change after the chemotherapy

DISCUSSION

The results of this study demonstrate how chemotherapy affects children with ALL in terms of their cognitive and linguistic abilities. Some children showed deterioration in verbal fluency, executive function, and language processing (Tables 1,2,3,4). These findings are consistent with other studies that indicate neurotoxicity from chemotherapy impacts the brain networks that underlie cognition and language abilities[15,16].

Chemotherapy-induced cognitive impairment (CICI) is a common long-term adverse effect among children who have survived leukemia, according to earlier research[17,18]. Working memory, attention, processing speed, and executive function, all essential for language processing and communication, are the most frequently impacted cognitive areas (Table 4). According to our research, children who showed a more significant loss in executive function also had difficulty with linguistic skills like discourse coherence, sentence construction, and word retrieval (Table 5). This supports the idea that chemotherapy impairs higher-order cognitive processes required for language use (Figure 2)[19,20].

In brain regions linked to language processing and executive function, such as the prefrontal cortex, hippocampus, and left temporal lobe, neuroimaging studies have shown that chemotherapy-induced neurotoxicity results in gray matter atrophy, decreased white matter integrity, and impaired neural connectivity[21]. There may be noticeable reductions in linguistic and cognitive capacities due to damage to these areas, which can affect phonological processing, syntactic comprehension, and spontaneous speech production[22].

Methotrexate and cytarabine, two chemotherapy drugs frequently used to treat leukemia, further aggravating cognitive-linguistic problems. These drugs have been linked to increased neuroinflammation, oxidative stress, and myelin breakdown. Younger patients, especially those in crucial stages of language acquisition, may experience delayed language development due to these neurotoxic consequences (Tables 1,2,3), increasing their vulnerability to long-term deficiencies in academic achievement and verbal communication (Figure 1)[23].

There is an urgent need for early screening and intervention measures because several children in this study severely decreased cognitive and verbal abilities. Although general cognitive rehabilitation is the main focus of current rehabilitation approaches for pediatric cancer survivors, our findings indicate that speech-language therapy (SLT) and cognitive-linguistic training may be required to address these children's unique linguistic challenges[24]. The findings showed that the change in REAL Scale results and IQ was not correlated with the age or sex of the participants (Table 6).

Language impairments brought on by chemotherapy may be alleviated using intervention techniques such as discourse-based language therapy, verbal fluency exercises, and memory-boosting activities[25]. Furthermore, non-pharmacological strategies such as transcranial direct current stimulation (tDCS), mindfulness-based treatment (MBT), and cognitive training have demonstrated promise in boosting neuroplasticity and promoting language function in young populations[26].

Future research should concentrate on longitudinal studies to evaluate the long-term development of chemotherapy-related cognitive and language impairments in childhood leukemia survivors. Examining early interventions' effects on language recovery may yield important information about successful treatment approaches[27]. Furthermore, more research on biological indicators of neurotoxicity and how they relate to language loss may aid in identifying patients who are at risk and creating individualized rehabilitation programs[28].

LIMITATIONS

The small sample size is one of the study's main limitations, impacting how broadly the results can be applied. Results from a more extensive and varied sample will be used in future studies. Furthermore, the study's follow-up time was only four months, which made it challenging to evaluate the long-term effect of chemotherapy. Future research should include a more extended follow-up period better to understand the long-term impact of the factors under study and consider potential delayed effects. The reliability and relevance of the results would be improved by increasing the sample size and lengthening the study period.

CONCLUSION

This study shows that pediatric leukemia chemotherapy can significantly affect a child's cognitive and linguistic development. Some children may notice a decline in executive functions, word retrieval, and fluency. These findings demonstrate the need for targeted cognitive-linguistic rehabilitation programs to support language development in cancer survivors. Future studies should continue to investigate efficient intervention techniques to lessen the neurocognitive effects of chemotherapy and improve the lives of children who have survived leukemia.

ABBREVIATIONS

ALL: Acute Lymphocytic Leukemia, **CICI:** Chemotherapy-induced cognitive impairment, **REAL Scale:** Receptive Expressive Arabic Language Scale, **SB-5:** The Stanford-Binet Intelligence Scales, **IQ:** Intelligent Quitient, **RLS:** Receptive language Score, **ELS:** Expressive Language Score, **TLS:** Total Language Score.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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